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**Epigenome-wide association of liver methylation patterns and complex metabolic traits in mice.**

**Journal:** Cell Metab

**Publication Year:** 2015

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**PubMed link:** 26039453

**Funding Grants:** CSUN-UCLA Bridges to Stem Cell Research

**Public Summary:**

We studied chemical modifications called DNA methylation in 90 differently laboratory strains of mice. We determined the association of DNA methylation with 68 different diseases or clinical traits such as bone density and insulin resistance. Our results indicate that natural variation in DNA methylation levels contributes to the cause of complex clinical traits.

**Scientific Abstract:**

Heritable epigenetic factors can contribute to complex disease etiology. Here we examine the contribution of DNA methylation to complex traits that are precursors to heart disease, diabetes, and osteoporosis. We profiled DNA methylation in the liver using bisulfite sequencing in 90 mouse inbred strains, genome-wide expression levels, proteomics, metabolomics, and 68 clinical traits and performed epigenome-wide association studies (EWAS). We found associations with numerous clinical traits including bone density, insulin resistance, expression, and protein and metabolite levels. A large proportion of associations were unique to EWAS and were not identified using GWAS. Methylation levels were regulated by genetics largely in cis, but we also found evidence of trans regulation, and we demonstrate that genetic variation in the methionine synthase reductase gene Mtrr affects methylation of hundreds of CpGs throughout the genome. Our results indicate that natural variation in methylation levels contributes to the etiology of complex clinical traits.

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